OPTIMAL>60, Improvement of Therapy of Elderly Patients With CD20+ DLBCL Using Rituximab Optimized and Liposomal Vincristine

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by University Hospital, Saarland

Sponsor:
University Hospital, Saarland

Collaborator:
German High-Grade Non-Hodgkin's Lymphoma Study Group

Information provided by (Responsible Party):
University Hospital, Saarland

ClinicalTrials.gov Identifier:
NCT01478542

First received: November 18, 2011
Last updated: August 13, 2015
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History of Changes

Purpose

The purpose of this study is to improve the outcome of elderly patients with CD20+ Aggressive B-Cell Lymphoma and to reduce the toxicity of standard used Immuno-Chemotherapy by using an optimised schedule of the monoclonal antibody Rituximab, substituting conventional by Liposomal Vincristine and by a PET-guided reduction of therapy.

Condition	Intervention	Phase
CD20+ Aggressive B-Cell Lymphoma	Drug: Conventional Vincristine Drug: Liposomal Vincristine Drug: Ricover-scheme rituximab Drug: optimised rituximab-schedule	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Factorial Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Improvement of Outcome and Reduction of Toxicity in Elderly Patients With CD20+ Aggressive B-Cell Lymphoma by an Optimised Schedule of the Monoclonal Antibody Rituximab, Substitution of Conventional by Liposomal Vincristine, and FDG-PET Based Reduction of Therapy.

Resource links provided by NLM:

MedlinePlus related topics: Lymphoma

Drug Information available for: Vincristine sulfate Rituximab

Genetic and Rare Diseases Information Center resources: B-cell Lymphomas Lymphosarcoma

U.S. FDA Resources

Further study details as provided by University Hospital, Saarland:

Primary Outcome Measures:

- Progression-free survival [Time Frame: 9 years] [Designated as safety issue: No]

  "OPTIMAL>60 Less Favourable": To test the effects of substitution of conventional by liposomal vincristine and of a 2-w eek applications of 8x rituximab by an optimised application of 12 x rituximab stratified log rank tests w ill be performed for each question (stratified for IPI-factors). Proportional hazard models w ill be used to investigate treatment interaction and to obtain estimates for the single treatment effects (HR) adjusting for the IPI-factors. "OPTIMAL>60 Favourable" Grade of neurotoxicity w ill be estimated and indicated w ith a 95% confidence interval (CI) separated to each type of vincristine. To investigate the 3-year PFS w ith 95% CI the Kaplan-Meier estimator w ill be used.

Secondary Outcome Measures:

- for efficacy: rate of complete remissions (CR-rate), rate of partial responses (PR-rate), rate of primary progressions, relapse rate, event-free survival (EFS) and overall survival (OS); rate and CTC grades of polyneuropathy. [Time Frame: 9 years]
  [Designated as safety issue: No]

  Secondary endpoints: To analyze how (i. e. in w hich direction) and how often a pre-treatment FDG-PET-based assignment (PET-0) w ould have affected the assignment of a patient to a different stage, IPI risk group or treatment, respectively. To compare the efficacy and side effects of the (post-induction therapy FDG-PET-based) individualised treatment strategy in OPTIMAL>60 w ith the fixed (pre-defined) treatment strategy in RICOVER-60. Rates and grades of polyneuropathy w ill be determined according to CTC-v4.03

Estimated Enrollment:	1152
Study Start Date:	November 2011
Estimated Study Completion Date:	October 2019
Estimated Primary Completion Date:	October 2016 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Favourable Prognosis F-A Induction therapy w ith 4 cycles of R-CHOP-14 (Rituximab 375 mg/sqm, Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, conventional Vincristine 1,4 mg/sqm [max. 2mg absolute], Predniso[lo]ne 100mg/d d1-5) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive 2 additional cycles of R-CHOP-14 + 2xR plus additional involved-site radiotherapy, if FDG-PET negative only 4xR w ithout radiotherapy.	Drug: Conventional Vincristine
Experimental: Favourable F-B Induction therapy w ith 4 cycles of R-CHLIP-14 (Rituximab 375 mg/sqm, Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, liposomal Vincristine 2 mg/sqm, Predniso[lo]ne 100mg/d d1-5) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive 2 additional cycles of R-CHLIP-14 + 2xR plus additional involved-site radiotherapy, if FDG-PET negative only 4xR w ithout radiotherapy.	Drug: Liposomal Vincristine
Active Comparator: Less Favourable LF-A Induction therapy w ith 6 cycles of R-CHOP-14 (Rituximab 375 mg/sqm, Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, conventional Vincristine 1,4 mg/sqm [max. 2mg absolute], Predniso[lo]ne 100mg/d d1-5) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive 2xR plus additional radiotherapy to the initial bulky region, if FDG-PET negative only 2xR w ithout radiotherapy. After 3xR-CHOP-14 an interim restaging w ill be performed.	Drug: Conventional Vincristine Drug: Ricover-scheme rituximab
Experimental: Less Favourable LF-B Induction therapy w ith 6 cycles of R-CHLIP-14 (Rituximab 375 mg/sqm, Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, liposomal Vincristine 2 mg/sqm, Predniso[lo]ne 100mg/d d1-5) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive 2xR plus additional radiotherapy to the initial bulky region, if FDG-PET negative only 2xR w ithout radiotherapy. After 3xR-CHLIP-14 an interim restaging w ill be performed.	Drug: Liposomal Vincristine Drug: Ricover-scheme rituximab
Experimental: Less Favourable LF-C Induction therapy w ith 6 cycles of CHOP-14 (Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, conventional Vincristine 1,4 mg/sqm [max. 2mg absolute], Predniso[lo]ne 100mg/d d1-5) combined w ith an optimized Rituximab-schedule (375 mg/sqm, d-4, d-1, d1, d4, d14, d28, d42, d56, d91, d126, d175, d238) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive additional radiotherapy to the initial bulky region, if FDG-PET negative omission of radiotherapy. After 3x CHOP-14 an interim restaging w ill be performed.	Drug: Conventional Vincristine Drug: optimised rituximab-schedule
Experimental: Less Favourable LF-D Induction therapy w ith 6 cycles of CHLIP-14 (Cyclophosphamide 750 mg/sqm, Doxorubicin 50 mg/sqm, liposomal Vincristine 2 mg/sqm, Predniso[lo]ne 100mg/d d1-5) combined w ith an optimised Rituximab-schedule (375 mg/sqm, d-4, d-1, d1, d4, d14, d28, d42, d56, d91, d126, d175, d238) and then definitive (post-induction) restaging w ith FDG-PET. If FDG-PET positive additional radiotherapy to the initial bulky region, if FDG-PET negative	Drug: Liposomal Vincristine Drug: optimised rituximab-schedule

omission of radiotherapy. After 3x CHLIP-14 an interim restaging w ill be performed.	

Detailed Description:
Primary objective of study:

"OPTIMAL>60 Less Favourable" Patients w ith less favourable prognosis:

1. To test w hether progression-free survival (PFS) can be improved by substituting conventional by liposomal vincristine;
2. To test w hether PFS can be improved by 12 optimised applications instead of 8 2-w eek applications of rituximab. "OPTIMAL>60 Favourable": Patients w ith favourable pro-gnosis:
3. Comparison of neurotoxicity of conventional and liposomal vincristine;
4. Determination of PFS for the treatment strategy of reducing treatment in patients w ith negative FDG-PET after 4 x R-CHOP/CHLIP-14 (PET-4) and comparison w ith the corresponding patient population in RICOVER-60. Secondary objectives: "OPTIMAL>60 Favourable" and "OPTIMAL>60 Less Favourable":
5. Comparison of the prognostic value of a pre-treatment FDG-PET (PET-0) w ith conventional CT/MRT.
6. Comparison of the FDG-PET-based individualised treatment strategy in OPTIMAL>60 w ith the fixed (pre-defined) treatment strategy in RICOVER>60.
7. Estimation of the vincristine-related neurotoxicity ("OPTIMAL>60 Less Favourable only, since vincristine related neurotoxicity is primary objective of the study in favourable patients) and other toxicities (all patients).
8. Determination of the therapeutic efficacy of a Vitamin D substitution by comparing the first patients w ithout Vitamin D substitution w ith patients w ith Vitamin D substitution.

Eligibility

Ages Eligible for Study:	61 Years to 80 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria
Inclusion Criteria:

1. Age: 61-80 years
2. All risk groups (IPI 1-5)
3. Diagnosis of aggressive CD20+ B-NHL, based on an excisional biopsy of a lymph node or on an appropriate sample of a lymph node or of an extranodal involvement. It w ill be possible to treat the follow ing entities in this study as defined by the new WHO classification of 200870: B-NHL:
   - Foll. lymphoma grade IIIb
   - DLBCL, not otherw ise specified (NOS)
     - common morphologic variants:
       - centroblastic
       - immunoblastic
       - anaplastic
     - rare morphologic variants
   - DLBCL subtypes/entities:
     - T-cell/histiocyte-rich large B-cell lymphoma
     - primary cutaneous DLBCL, leg type
     - EBV-pos. DLBCL of the elderly
   - DLBCL associated w ith chronic inflammation
   - primary mediastinal (thymic) LBCL
   - intravascular large B-cell-lymphoma
   - ALK-positive large B-cell-lymphoma
   - plasmoblastic lymphoma
   - primary effusion lymphoma
   - secondary or simultaneous high grade B-cell-lymphoma
   - B-cell lymphoma, unclassifiable, w ith features intermediate betw een DLBCL and Burkitt lymphoma
   - B-cell lymphoma, unclassifiable, w ith features intermediate betw een DLCBL and Hodgkin lymphoma
4. Performance status ECOG 0 - 2 after prephase treatment. The performance status of each patient must be assessed before the initiation and after the end of prephase treatment w hich, as experience has show n, can result in a significant improvement of the

patient's performance status. The pre-treatment performance status which can range from ECOG 0 to ECOG 4 must be documented in the Staging CRF (see ISF); the performance status after the prephase treatment must be documented in the respective Prephase Treatment CRF (PT form: see ISF). A definition of the performance status is provided in Appendix 28.10.

5. Written informed consent of the patient
6. Contract of participation signed by the study centre and sponsor

Exclusion Criteria:

1. Already initiated lymphoma therapy (except for the prephase treatment)
2. Serious accompanying disorder or impaired organ function (except when due to lymphoma involvement), in particular:
   - heart: angina pectoris CCS >2, cardiac failure e.g. NYHA >2 and/or EF <50% or FS<25% in nuclear medicine examination/echocardiography
   - lungs: if respiratory problems are suspected the patient is to be excluded if the resultant pulmonary function test shows FeV1<50% or a diffusion capacity <50% of the reference values
   - kidneys: creatinine >2 times the upper reference limit
   - liver: bilirubin >2 times the upper reference limit, aspartate transaminase (AST, SGOT) or alanine transaminase (ALT, SGPT) >3 x institutional upper reference limit
   - uncontrollable diabetes mellitus (prephase treatment with predniso[lo]ne!)
3. Platelets <75 000/mm3, leukocytes <2 500/mm3 (if not due to lymphoma)
4. Known hypersensitivity to the medications to be used
5. Known HIV-positivity
6. Patients with severe impairment of immune defense
7. Patients with constipation with imminent risk of ileus
8. Chronic active hepatitis
9. Poor patient compliance
10. Simultaneous participation in other treatment studies or in another clinical trial within the last 6 months
11. Prior chemo- or radiotherapy, long-term use of corticosteroids or anti-neoplastic drugs for previous disorder
12. Other concomitant tumour disease and/or tumour disease in the past 5 years (except basalioma of the skin and carcinoma in situ)
13. CNS involvement of lymphoma (intracerebral, meningeal, intraspinal intradural) or primary CNS lymphoma
14. Persistent neuropathy grade ≥2 (NCI CTC-AE v4.03) (unless due to lymphoma involvement)
15. History of persistent active neurologic disorders grade >2 including demyelinating form of Charcot-Marie-Tooth syndrome, acquired demyelinating disorders, or other demyelinating condition
16. Pregnancy or breast-feeding women
17. Active serious infections not controlled by oral and/or intravenous antibiotics or anti-fungal medication
18. Any medical condition which in the opinion of the investigator places the subject at an unacceptably high risk for toxicities.
19. MALT lymphoma
20. Non-conformity to eligibility criteria
21. Persons not able to understand the impact, nature, risks and consequences of the trial (including language barrier)
22. Persons not agreeing to the transmission of their pseudonymous data
23. Persons depending on sponsor or investigator
24. Persons from highly protected groups. Pts. with CNS lymphoma should not be included in this study.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01478542

Contacts

Contact: DSHNHL Central Study Office +4968411623084 DSHNHL@uks.eu

Show 127 Study Locations

Sponsors and Collaborators

University Hospital, Saarland

German High-Grade Non-Hodgkin's Lymphoma Study Group

Investigators

Principal Investigator: Michael G. Pfreundschuh, Professor Saarland University, Saarland University Hospital

More Information

No publications provided

Responsible Party:	University Hospital, Saarland
ClinicalTrials.gov Identifier:	NCT01478542 History of Changes
Other Study ID Numbers:	**DSHNHL 2009-1**
Study First Received:	November 18, 2011
Last Updated:	August 13, 2015
Health Authority:	Germany: Ethics Commission Germany: Federal Institute for Drugs and Medical Devices

Keywords provided by University Hospital, Saarland:

DLBCL	FDG-PET
Liposomal Vincristine (Marqibo)	Bulky Disease
Optimised Rituximab	Radiation
Toxicity	age >60 years
Elderly Patients	First line Therapy

Additional relevant MeSH terms:

Aggression	Vincristine
Lymphoma, B-Cell	Antimitotic Agents
Behavioral Symptoms	Antineoplastic Agents
Immune System Diseases	Antineoplastic Agents, Phytogenic
Immunoproliferative Disorders	Antirheumatic Agents
Lymphatic Diseases	Immunologic Factors
Lymphoma	Mitosis Modulators
Lymphoma, Non-Hodgkin	Molecular Mechanisms of Pharmacological Action
Lymphoproliferative Disorders	Pharmacologic Actions
Neoplasms	Physiological Effects of Drugs
Neoplasms by Histologic Type	Therapeutic Uses
Rituximab	Tubulin Modulators

ClinicalTrials.gov processed this record on October 02, 2015